

CARBON-14 AND TRITIUM ISOTOPE EFFECTS IN HOFMANN DEGRADATION OF QUARTERNARY AMINES

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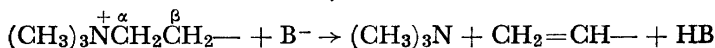
INTRODUCTION

At the time we started the following studies there were only a few measurements of isotope effects in *E2* reactions of the Hofmann elimination type. Saunders and Asperger¹ have found that substitution of ³⁴S for ³²S in the base-catalysed elimination reaction of $C_6H_5CH_2CH_2\overset{+}{S}(CH_3)_2Br^-$ results in a negligible kinetic isotope effect, indicating that the activation process in the rate-determining step involves practically no stretching of the C-S bond in the transition state. Later, Saunders and Edison² determined the deuterium isotope effects for *E2* eliminations on compounds of the type $C_6H_5CD_2CH_2X$ with $X = \overset{+}{S}(CH_3)_2$ and $X = \overset{+}{N}(CH_3)_3$.

Hodnett and Flynn³ measured the isotope effect for trimethyl-(*p*-nitro- β -phenethyl- β -T)-ammonium iodide and found $k_H/k_T = 7.4 \pm 2.8$. Shiner and Smith⁴ degraded trimethyl-ethyl- β -D₃-ammonium hydroxide and obtained the value $k_H/k_D = 3.9 \pm 0.5$ at 137°. A few months ago Ayrey, Fourns *et al.*⁵ published the measurements of nitrogen isotope effects for ethyl-trimethylammonium-¹⁵N hydroxide and trimethyl- β -phenethyl-ammonium-¹⁵N hydroxide.

We determined the carbon-14 and tritium isotope effects for the following quarternary ammonium hydroxides:

- $(CH_3)_3\overset{+}{N}R, OH^-$
- (I) R = $-^{14}CH_2CH_3$
 - (II) R = $-^{14}CH_2CH_2CH_3$
 - (III) R = $-^{14}CH_2CH_2C_6H_4NO_2(p)$
 - (IV) R = $-^{14}C(CH_3)_3$
 - (V) R = $-CH_2-^{14}CH_2CH_3$
 - (VI) R = $-CHTCH_2CH_3$
 - (VII) R = $-CH_2CHTCH_3$
 - (VIII) R = $-CH_2CH_2CH_2T$
 - (IX) R = $-CH_2CH_2T$
 - (X) R = $-CH_2CHTC_6H_4NO_2(p)$



At first we were interested in determining whether there are measurable carbon-14 isotope effects and if this is the case, to compare their relative

magnitudes. Although it was recognized by Ingold as early as 1927 that *E2* reactions need not be fully synchronous processes, only recently has this concept been discussed. Bunnett⁶ has given an excellent review. There should be a pronounced difference between the carbon-14 isotope effect of (I) and (II) on the one hand and (III) on the other. Correspondingly, there should be a difference in intramolecular tritium isotope effects of (VII) and (IX) as compared to that of (X), if the concept of a continuous spectrum of *E2* reactions differing in the relative extent of C-N and C_β-H bond rupture in the transition state is correct. The determination of the isotope effect of (IV) was of interest because in *S_N1* reactions the tertiary butyl group shows only a very small or even inverse carbon-14 isotope effect.

The measurements of the secondary isotope effects of (VI) and (VIII) were performed in order to get some additional insight into the transition state.

METHODS⁷

The labelled ammonium salts were prepared by the usual techniques. The corresponding iodides were added to trimethylamine. All ethyl- and propyl-iodides were purified by gas chromatography. (III) was prepared by the Mannich reaction of formaldehyde-¹⁴C, *p*-nitrophenylacetic acid and dimethylamine. The formed 3-dimethylamino-2-*p*-nitro-phenylpropionic acid was decarboxylated and the resulting amine quarternized with methyl iodide.

In the preparation of (IV), *t*-butyl alcohol-¹⁴C was added to sodium cyanide according to Ritter and the resulting *t*-butyl formamide was reduced with lithium aluminium hydride to give *t*-butyl methylamine, which was methylated according to Leuckart to the tertiary amine and then quarternized with methyl iodide.

All ammonium compounds were repeatedly recrystallized in form of their tetraphenyl borates and/or picrates to constant specific radioactivity.

Elimination procedures

A series of experiments was carried out to check the extent to which side reactions, hydrogen exchange *etc.* take place under elimination conditions⁷. When a solvent was used for running the elimination reaction of trimethylpropyl- α -¹⁴C-ammonium hydroxide, 80 per cent substitution occurred⁷. The reaction proceeded without substitution at a reasonable rate when the melted ammonium-base hydrates were heated to 40 or 60° at a pressure of 30 microns.

The selected methods for the different compounds are shown in *Table 1*.

Determination of the isotope effects

Three methods were used to determine the isotope effects⁸:

- A: Comparison of the molar specific activity of reactant remaining after a measured percentage reaction;
- B: Comparison of the molar specific activity of the accumulated reaction product up to a measured percentage reaction with the specific activity of the starting material;

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Table 1. Reaction conditions for elimination and methods of isotope effect determination

Compound	Method of isotope effect determination	Elimination conditions	
		Temperature (°C)	Solvent and base
(I)	A	139	Diethylene glycol, diethylene glycolate
(I)	C	40	Melted hydrate of ammonium hydroxide, vacuum
(II)	A, C	50	Melted hydrate of ammonium hydroxide, vacuum
(III)	A	100	Phosphate buffer, pH 7
(IV)	A, B	91	Triethylene glycol
(V)	A	51	Melted hydrate of ammonium hydroxide, vacuum
(VI)	C	50	Melted hydrate of ammonium hydroxide, vacuum
(VII)	C	60	Melted hydrate of ammonium hydroxide, vacuum
(VIII)	A, C	40, 60, 80	Melted hydrate of ammonium hydroxide, vacuum
(IX)	C	60	Melted hydrate of ammonium hydroxide, vacuum
(IX)	—	130	Triethylene glycol
(X)	A	22	Methanol, methoxide

C: Comparison of the molar specific activity of a small increment of product formed at a specific time during a reaction with the molar specific activity of the starting material.

As shown in Tables 2 and 3 the measurements are mostly repeated 3 to 7 times.

RESULTS AND DISCUSSION

The results of the isotope effect measurements for the carbon-14 labelled compounds are given in Table 2. In every case a clear effect has been found, proving that the C-N bond rupture occurs in the rate determining step. A calculation of the maximum value ($k_{12C}/k_{14C} = 1.15$ at 40°) which could be expected is reached in the case of (I), (II) and (IV) to the extent of one-half to one-third. The tertiary butyl group shows a normal behaviour in contrast to S_N1 reactions. There seems to be no extreme shift to a carbonium ion mechanism. The isotope effect of (III) is drastically smaller than that obtained for (I), (II) and (IV). There may be a shift to a carbanion mechanism. These results are in good agreement with the nitrogen-15 isotope effects reported by Ayrey, Bourns *et al.*⁵ who found for trimethylphenethyl-ammonium hydroxide a value which is a little less than one third, and for trimethyl-ethyl-ammonium hydroxide about one half of the theoretical maximum effect. These results show clearly that the C-N bond rupture must be more fully advanced in the transition state than is C-S bond rupture for the sulphonium salts.

In Table 3 our results of the tritium isotope effects together with other known hydrogen isotope effects of Hofmann elimination are shown. For better comparison in one column all ratios are calculated for k_H/k_T at 60° .

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Table 2. Carbon-14 isotope effects

Compound	Temperature (°C)	$k_{^{12}\text{C}}/k_{^{14}\text{C}}$	Error ^a	Isotope effect calculated for 40°
— ¹⁴ CH ₂ CH ₃	139	1.033 ^b	±0.004	1.05
— ¹⁴ CH ₂ CH ₃	40	1.065 ^c	—	1.06
— ¹⁴ CH ₂ CH ₂ CH ₃	50	1.075 ^d	±0.006	1.08
		1.067 ^e	—	1.07
		1.066 ^e	—	
— ¹⁴ CH ₂ CH ₂ C ₆ H ₄ (<i>p</i>)NO ₂	100	1.026 ^f	±0.003	1.03
— ¹⁴ C(CH ₃) ₃	91	1.052 ^g	—	1.06
		1.058 ^e	—	
		1.045 ^e	—	
—CH ₂ ¹⁴ CH ₂ CH ₃	51	1.040 ^g	±0.005–0.01	1.03 ₅
		1.032 ^g	±0.005–0.01	

^a Average error from average.^b Average from 7 independent experiments.^c Average from 5 determinations.^d Average from 4 determinations.^e Single determination error calculation ±0.005–0.01.^f Average from 6 independent experiments.^g Single determination.

Table 3. Tritium and deuterium isotope effects

Compound	Temperature (°C)	$k_{\text{H}}/k_{\text{H}}^*$	Error ^a	Isotope effect calculated for $k_{\text{H}}/k_{\text{T}}$ at 60°
—CHTCH ₂ CH ₃	50	1.10 ^b	±0.006	2.9
—CH ₂ CHTCH ₃	60	2.86 ^c	±0.045	
	Kinetic	2.00 ^e	±0.02	
	Secondary	1.33		
—CH ₂ CH ₂ CH ₂ T	40	1.12	±0.007	2.96
	60	1.11 ^d		
	80	1.13		
—CH ₂ CH ₂ T	60	2.96 ^b	±0.2	2.9
	Kinetic	1.60	±0.05	
	Secondary	1.26	±0.03	
	130 Kinetic	1.23	±0.05	
			+4	
—CH ₂ CHTC ₆ H ₄ (<i>p</i>)NO ₂	22	13 ^e	—2.5	8 ± 1.6(12.3 ± 4) ^a
	Kinetic	2.20	±0.20 ^f	
	Secondary	1.18	±0.10 ^f	
—CH ₃ CD ₃	137	3.90 ⁴		13.8
—CH ₂ CH ₂ C ₆ H ₅	50	2.98 ³		3.9

^a Average error from average.^b Average from 4 and 5 determinations from two independent experiments.^c Average from 4 different experiments.^d Average from 5 experiments and 8 determinations.^e Average from 3 determinations.^f The corresponding values reported by Hodnett and Flynn³ are 2.03 and 1.15.

There may be two reasons for the secondary isotope effect of 1.10 for trimethyl-propyl- α -T-ammonium hydroxide (VI): (a) the change in hybridization in going from sp^3 to sp^2 , and (b) the higher inductive effect of a C–T bond compared with a C–H bond. By this phenomenon the electron

density is increased at the α -carbon atom and as a consequence the C-C double bond is less easily formed. The change in the inductive effect should be of less influence however because the isopropyl residue (methyl group in α position!) is eliminated only 1.4 times slower than the ethyl residue⁹. Therefore, the secondary isotope effect seems to be brought about by the change in hybridization. Streitwieser *et al.*¹⁰ calculated for such an effect a k_H/k_D value of 1.30. Therefore, one should expect for k_H/k_T a value of 1.46¹¹. The isotope effect of 1.10 which was found is much smaller *i.e.* the transition state has little sp^2 character. Asperger *et al.*¹² determined the secondary isotope effect for the *E2* reaction of 2-phenyl-ethyl-1-¹-D₂-bromide. The value for $k_H/k_D = 1.17$, that means there is more sp^2 character in the transition state. The secondary isotope effect found for trimethyl-propyl- β -T-ammonium hydroxide $k_H/k_T = 1.33$ can also be explained by the change from sp^3 to sp^2 and the larger inductive effect of the C-T bond. The increased inductive effect is now however of greater influence. This can be seen from the fact that the n-propyl residue is eliminated 27 times slower than the ethyl residue⁹. This decrease in the elimination rate is of course partly due to steric effects.

The secondary isotope effect $k_H/k_T = 1.11$ of trimethyl-propyl- γ -T-ammonium hydroxide may be explained by the greater inductive effect of a CH₂T group compared with a CH₃ group. Of special interest is the comparison of the primary isotope effects of trimethyl-ethyl- β -T and trimethyl-propyl- β -T-ammonium hydroxide with that of *p*-nitrophenethyl- β -T-trimethylammonium hydroxide. There is a drastic increase in going from 2.9 to 8 ± 1.6 . The value for the *p*-nitrophenethyl compound was already determined by Hodnett and Flynn³, who found a value of 12.3 ± 4 for the elimination in acetate buffer at pH 7, calculated for 60°. Both measurements show that there is a high isotope effect compared to alkyl compounds.

From the relative magnitudes of the intramolecular tritium isotope effects found in the reactions of the three ammonium salts one should be able to get information concerning the extent to which the proton is transferred from carbon to the base at the transition state. If for both ammonium compounds it is more than half transferred, then that reaction in which C-H bond weakening is greater, will give the smaller tritium isotope effect. If, on the other hand, the proton is less than half transferred the opposite will be the case.

The values found, show clearly that the latter seems to be the case, because the C-H bond stretching in the transition state should be less for the alkyl compounds than for the *p*-nitrophenethyl compound.

The relative values of the carbon-14 isotope effects for the three compounds (I, II and III, *Table 1*) show that the two bond changes are complementary; *i.e.* the less C $_{\beta}$ -H bond rupture the more N-¹⁴C bond rupture in the transition state.

There is a remarkable disagreement in the intramolecular isotope effect k_H/k_T of (IX) with that reported by Shiner and Smith⁴ for trimethyl-ethyl- β -D₃-ammonium hydroxide. The value k_H/k_D measured at 137° would correspond to the calculated k_H/k_T at 60° of about 13 (*Table 3*). As might be expected, the value for k_H/k_D reported by Saunders and Asperger¹ for trimethyl-phenethyl- β -D₂-ammonium hydroxide (*Table 3*) lies between

that for alkyl compounds and the *p*-nitrophenethyl compound. This means that for the phenethyl compound, the C-H bond rupture in the transition state is less than half.

Using the values $k_{\text{H}}/k_{\text{D}}$ of trimethyl-ethyl- β -D₃-ammonium hydroxide and trimethyl-phenethyl- β -D₂-ammonium hydroxide Ayrey, Bourns *et al.*⁵ concluded that in the case of the ethyl compound the proton is about half transferred to the attacking base and that in the case of the phenethyl compound C-H bond weakening in the transition state is already much greater.

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